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Synthesis of 4-amino substituted 1,8-naphthalimide derivatives using palladium-mediated amination

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ABSTRACT

Successful amination of 4-bromo-1,8-naphthalimides with 'lengthy' imide *N*-functionality has been achieved using a general palladium mediated approach (conventional thermal protocols were sub-optimal). Only readily available Pd/ligand combinations were considered and the resulting Buchwald–Hartwig procedure using $Pd_2(dba)_3$, Xantphos and Cs_2CO_3 is high yielding, relatively mild (40–80 °C, 24 h, yields 50–90%), requires only a modest excess of amine (3.0 equiv) and works equally well with other imide N-substituents. As such, the protocol complements existing methods but is superior for more complex substrates. Herein we compare this Pd mediated approach to the methods most commonly used and further demonstrate its utility by synthesising a number of new, highly fluorescent, 4-aminonaphthalimides.

1. Introduction

Historically, 4-amino-1,8-naphthalimides have been widely employed as components of fluorescent dyes [1]. More recently, these fluorophores have been used in a number of more specialist applications including; cellular imaging [2], DNA intercalation [3] and supramolecular chemistry [4]. With these more sophisticated end uses, higher levels of structural complexity is required. Therefore, more advanced and practical methodology for the synthesis of substituted naphthalimides is necessary. Established methods employed for the synthesis of 4-amino-1,8-naphthalimide derivatives involve nucleophilic aromatic substitution by either (i) heating (≥100 °C) 4-halo-naphthalimides with the desired amine [5] or (ii) treating 4-nitro-naphthalimide with the amine in DMF at 21 °C (Fig. 1) [6]. While the use of copper catalysts to aid the transformation has been known for some time (Ullmann condensation) [7], it is only recently that a handful of examples of palladium mediated coupling of anilines have also emerged to access highly specific 4-arylamino-1,8-naphthalimide derivatives [8]. Herein, we describe a general, high yielding, Buchwald–Hartwig cross coupling protocol for the synthesis of 4-amino-1,8-naphthalimde derivatives using $Pd_2(dba)_3$ and Xantphos—one of the most readily available (and affordable) Pd source and ligand combinations known.

2. Results and discussion

Substitution reactions of *N*-ethyl-4-bromo-1,8-naphthalimide (**1**) are usually accomplished using nucleophilic aromatic substitution (S_NAr) [9–11]. For example, nucleophilic substitution of 4-bromonaphthalimide **1** with morpholine (5.0 equiv.) afforded the 4-amino derivative **3** (83%) after heating by microwave irradiation at 100 °C for 4 h (Scheme 1). Unfortunately it is our experience that this method gives poor yields with longer/larger *N*-alkyl imide substituents. Indeed, when a solution of *N*-heptyl naphthalimide **2**, morpholine (5.0 equiv) and Et_3N in EtOH was heated by microwave irradiation at 100 °C for 4 h poor conversion of starting materials was observed and only 40% of the desired 4-amino-1,8-naphthalimide derivative **4** was isolated (Scheme 1). While exceptions exist in the literature [12], protocols for the synthesis of related imides generally require the use of high boiling solvents (eg. 1,4-dioxane or 2-methoxyethanol), high temperatures (≥100 °C) [5] and a large excess of amine (≥10 equiv) [13]. Such reaction conditions are not always practical.

When the *N*-imide substituent contained additional functionality such as an ester (for example, imide **7** formed in 92% yield by the condensation of commercially available 1,8-naphthalic anhydride **5** with methyl 6-aminohexanoate hydrochloride), the S_NAr

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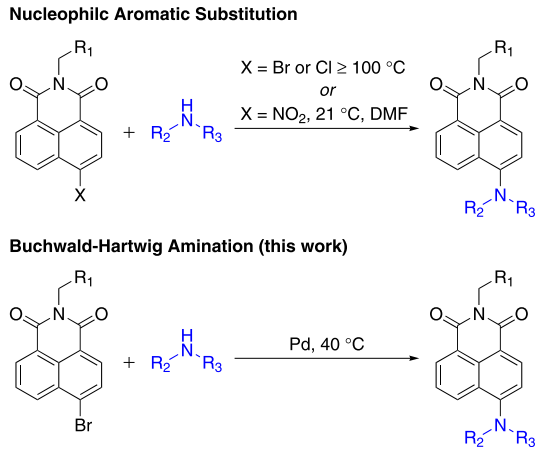
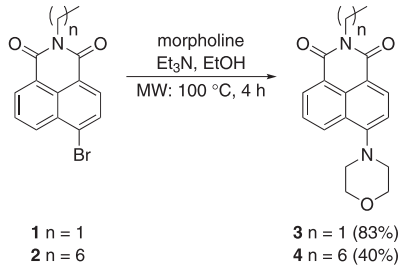


Fig. 1. Comparison of methodology for synthesis of 4-amino-1,8-naphthalimide derivatives. *Top*: existing S_NAr approaches [9–11], *Bottom*: Buchwald–Hartwig amination.



Scheme 1. Nucleophilic aromatic substitution of 4-bromo naphthalimide derivatives with morpholine highlighting the lower yields obtained when longer *N*-substituents are present.

reaction again gave low yields (Scheme 2). Indeed, only 45% of the desired 4-amino-1,8-naphthalimide **9** was isolated after heating 4-bromo naphthalimide **7** with morpholine (5.0 equiv) at 100 °C in EtOH using microwave irradiation. A conventional thermal method was also trialled but again little conversion was noted (<25% after 24 h). In addition to isolating the desired 4-amino-1,8-naphthalimide derivative **9**, amidation of the methyl ester was also observed (**10**, Scheme 2, X = Br, see Supporting Information Figs. S11 and S12).

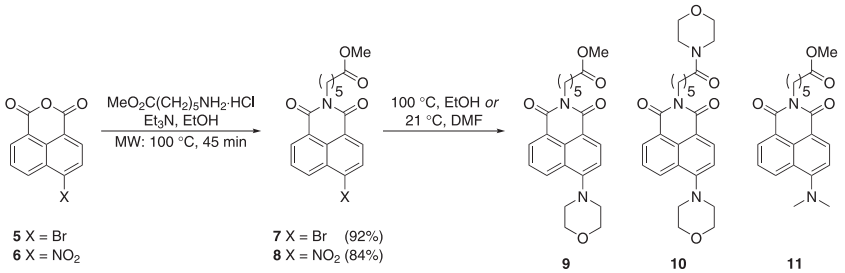
Moneva et al. described the successful amination of 4-nitro-*N*-phenyl substituted 1,8-naphthalimide derivatives using *N*-allylamines in DMF at 21 °C (Scheme 2, X = NO_2) [6]. Unfortunately, in our hands, the use of the 4-nitro-1,8-naphthalimide derivative **8** also gave poor conversion and low isolated yields (≤20%). Only when the temperature was increased to 80 °C were all starting materials consumed. Nevertheless, even with full consumption of starting material, poor mass recovery and low isolated yields (≤20%) resulted. In addition, another undesired side reaction occurred, which gave small amounts of the 4-dimethylamino product **11** (Scheme 2, see Supporting Information, Figs. S13 and S14) [14].

An alternate methodology involving palladium-catalysed Buchwald–Hartwig cross-coupling was pursued. While a handful of examples exist in which a palladium mediated approach for coupling of specific aromatic amines, anilines and carbazoles with 4-bromo-1,8-naphthalimide derivatives have been reported [8], the reaction conditions vary considerably with each substrate. As such, a more general protocol was sought that would be practical for a range of anilines and amines (both 1° and 2°).

A plethora of possible palladium sources and phosphine ligand combinations are available for Buchwald–Hartwig cross-coupling reactions [15–19] and while many are very high yielding they require either an expensive catalyst/ligand combination or the synthesis of a specialist ligand [20]. As our aim was to develop a protocol that would be more cost effective and user friendly only a selection of common Pd catalysts and readily available ligands were trialled (Table 1). In the initial reaction $Pd(OAc)_2$ (2 mol%), PPh_3 (4 mol%), 4-bromo-1,8-naphthalimide **7**, morpholine and NaO^tBu were heated in toluene for 24 h at 40 °C (Table 1, Entry 1). Whilst the yield for this reaction was poor (5%), formation of the desired compound occurred at low temperature (40 °C) and the previously discussed side products associated with high reaction temperatures were not observed. After screening a small number of palladium and ligand combinations (Entries 1–9), it became clear that (with the exception of dppf, Entry 7) bulky bidentate bisphosphines, such as (*S*)-BINAP and Xantphos were the ligands of choice (35% and 40% yields, Entries 8 and 9 respectively).

Further investigation into the effect of the palladium/ligand (Pd/L) ratio was conducted using (*S*)-BINAP and Xantphos as the ligands. Lower yields were observed when a Pd/L ratio of 1:2 was used (Table 1, Entries 10 and 11) instead of 1:1 (Entries 8 and 9). However, the 2:1 combination of $Pd_2(dba)_3{\cdot}CHCl_3$ (4 mol%) and Xantphos (4 mol%) with NaO^tBu gave the desired adduct in 50% isolated yield (Entry 12). Even though (*S*)-BINAP proved to be as effective as Xantphos (Entry 13), in our hands, Xantphos was removed more easily than (*S*)-BINAP during chromatographic purification and was therefore chosen for further studies.

The use of Cs_2CO_3 is reported to provide a cleaner reaction profile in Buchwald–Hartwig reactions [16] and when Cs_2CO_3 (2 equiv) was used in place of NaO^tBu (2 equiv) in the amination of bromonaphthalimide **7** (Entry 15) the reaction mixture indeed contained fewer by-products according to TLC analysis, however, the isolated yield of product was significantly lower (24%). Nevertheless, when 3 equivalents of Cs_2CO_3 was used, the reaction proceeded smoothly and the desired 4-morpholino naphthalimide **9** was isolated in 90% (Entry 16), which corresponds to an overall yield of 83% over two steps from naphthalic anhydride **5**. This compares favourably to the 43% overall yield in the previously reported two step synthesis of 4-morpholino naphthalimide **9** using



Scheme 2. Synthesis of 4-amino derivative **9** by nucleophilic aromatic substitution: X = Br, morpholine (5.0 equiv), Et_3N, EtOH, MW 100 °C, 4 h (≤45%); X = NO_2, morpholine, DMF, 21 °C, 24 h (≤20%).